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Hepatitis B immunoglobulin injection in pregnancy to interrupt hepatitis B virus mother-to-child transmission—a meta-analysis

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SUMMARY

Objectives: To evaluate the efficacy and safety of using hepatitis B immunoglobulin (HBIG) during pregnancy to prevent hepatitis B virus (HBV) mother-to-child transmission (MTCT).
Methods: We systematically reviewed the effect of HBIG in decreasing HBV MTCT from randomized controlled trials (RCTs) carried out between January 1990 and December 2008, in English and Chinese languages. Multiple databases were searched, and experts in this field were contacted. The methodological quality of each RCT was assessed by the Jadad score. We abstracted data on HBV intrauterine infection, MTCT, treatment methods, newborn immune prophylaxis methods, and adverse effects. A Mantel–Haenszel random-effects model was employed for all analyses using odds ratios (OR) and 95% confidence intervals (95% CI).
Results: Five thousand nine hundred newborns of asymptomatic hepatitis B surface antigen (HBsAg)-seropositive mothers from 37 qualified RCTs were included. Compared with the control group, newborns in the HBIG group had a lower intrauterine infection rate (indicated by HBsAg as OR 0.22, 95% CI [0.17, 0.29], from 32 RCTs; indicated by HBV DNA as OR 0.15, 95% CI [0.07, 0.30], from 13 RCTs; $p < 0.01$ for both) and a higher protection rate (indicated by hepatitis B surface antibody (HBsAb) as OR 11.79, 95% CI [4.69, 29.61], from 15 RCTs; $p < 0.01$). The same trend was found in MTCT by the time of 9–12 months after birth, indicated by HBsAg (OR 0.33, 95% CI [0.21, 0.51], from nine RCTs; $p < 0.01$) and HBsAb (OR 2.49, 95% CI [1.55, 4.01], from 11 RCTs; $p < 0.01$). HBIG appears to be safe, but a few RCTs have reported adverse events.
Conclusion: Multiple injections of HBIG in HBV carrier mothers with a high degree of infectiousness in late pregnancy, effectively and safely prevent HBV intrauterine transmission.

1. Introduction

The World Health Organization (WHO) reports that, worldwide, there are over two billion people who have a past or present hepatitis B virus (HBV) infection, and 350 million of them are chronic HBV carriers.[1] Mother-to-child transmission (MTCT) accounts for 40–50% of HBV carriers.[2] Joint HBV immune prophylaxis with hepatitis B vaccine (HBVac) and hepatitis B immunoglobulin (HBIG) beginning after birth, generally interrupts HBV MTCT during and after labor, and is recommended by the WHO, World Gastroenterology Organisation (WGO), and the US Centers for Disease Control and Prevention (CDC); however, none of these organizations have mentioned any schedule of HBIG medication in pregnant HBV carrier mothers.[3–5] Of the offspring of HBV carrier mothers, 1–8% suffer from HBV infection in their early life, even after they have received routine joint immune prophylaxis, because they were already infected in utero.[6,7]

It has been suggested that multiple small doses of HBIG intramuscular injection in HBV carrier mothers during pregnancy can effectively reduce intrauterine infection, which might be due to the reduced maternal HBV DNA load or the development of the newborn's passive immunity. However, even when treated with HBIG, the intrauterine infection rate is not significantly reduced in women with a high HBV DNA serum load.[8] Moreover, there remains controversy regarding the efficacy (whether there is the same efficacy in HBV carrier mothers with different degrees of infectiousness), safety (HBIG derives from blood), and HBV mutation-generating effects of HBIG.

We systematically reviewed the efficacy of HBIG treatment during late pregnancy together with joint immune prophylaxis after birth versus joint immune prophylaxis alone, in decreasing HBV MTCT, and investigated the safety of HBIG in pregnant women and their newborns.

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2. Methods

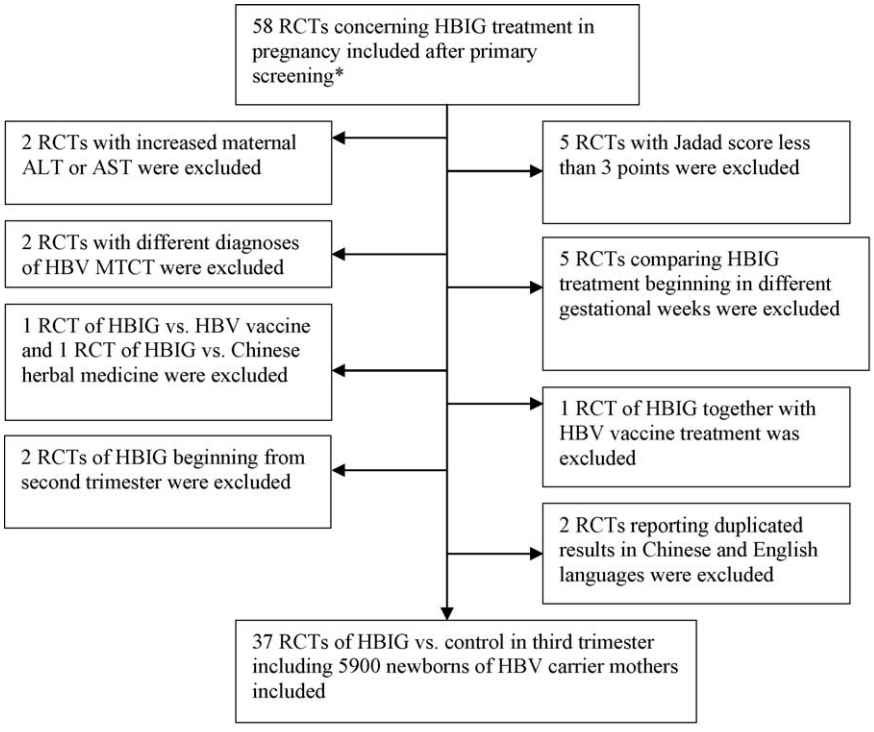
2.1. Study description

We searched the databases of Medline, EMBASE, the Cochrane Library, the National Science Digital Library (NSDL), and the China Biological Medicine Database (CBMdisc), January 1990 to December 2008, for relevant randomized controlled trials (RCTs) in the English language and Chinese peer-reviewed literature. Articles on an HBIG regimen in pregnant asymptomatic HBV carrier mothers, aimed at decreasing the risk of HBV MTCT, compared with placebo or no intervention during pregnancy (control), were sought. Keywords employed were HBIG (or hepatitis B immunoglobulin) and HBV (or hepatitis B virus) and intrauterine (or pregnant or pregnancy or mother or children or infant or newborn). We also hand-searched the bibliographies of the original studies, reviews (including meta-analyses), and relevant conference abstracts, and contacted some investigators in this field. The included RCTs were also required to have a clear description of HBV intrauterine transmission and MTCT, characteristics of the enrolled mothers, a description of recruitment methods, details of HBIG medication, newborn and infant immune prophylaxis schedules, and follow-up of both mothers and their children. Generally, HBV carrier mothers in the treatment group received 100–400 IU HBIG intramuscular injections once a month from 28 weeks of gestation or later for a total of three doses. All newborns (both in the treatment group and control group) received HBIG and HBVac joint immune prophylaxis after birth, as recommended by the WHO.

Two authors independently selected relevant studies and made a post-hoc assessment of methodological quality by means of the Jadad score, a procedure to independently assess the methodological quality of clinical trials, the score of which is between zero (very poor quality) and 5 (rigorous).[9] Questionable RCTs were discussed among all authors and/or further contact was made with the authors of the original RCTs to determine inclusion. The included mothers were all hepatitis B surface antigen (HBsAg)-positive and asymptomatic, without other diseases or medications during pregnancy. We abstracted data on study design and methods, inclusion and exclusion criteria, characteristics of patients, duration and dosage of HBIG regimens, outcomes, complications, and adverse events. Since HBV mothers with HBeAg and/or HBV DNA seropositivity have a higher degree of infectiousness, we sub-divided each comparison according to these indices.

2.2. End points and definitions

For primary outcomes, we estimated the rate of infant HBV infection (indicated by HBsAg or HBV DNA) or protection (indicated by hepatitis B surface antibody (HBsAb), the observed proportion) at various time-points (within 24 h after birth and at 9–12 months of age). In the included RCTs, the diagnosis of HBV



*Only RCTs were selected. RCTs from non-peer-reviewed journals were excluded; RCTs that did not meet the criteria set in the search section were excluded; RCTs without enough information on patient clinical condition, baseline, treatment of newborns, or follow-up were excluded.

(HBIG, hepatitis B immunoglobulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MTCT; mother-to-child transmission.)

Figure 1. Flow chart of analysis procedure.

Table 1
Characteristics of randomized controlled trials

Reference RCT[a]	Maternal		HBIG treatment		Newborn[b]			9–12 month infant[b]			
	HBeAg	DNA	Dose	Time	HBsAg-pos	DNA-pos	HBsAb-pos	HBsAg-pos	DNA-pos	HBsAb-pos	Jadad score
1. Chen 2003	+/−	+/−	200 IU	28, 32, 36 weeks		U 1/26:2/20[d] U 2/18:6/15[e] U 3/14:8/12[f]					2/3[g]
2. Chen 2006	N	N	200 IU	28, 32, 36 weeks	5/45:10/40	3/45:5/40					3
3. Chen 2006-II	+/−	N	200 IU	28, 32, 36 weeks	U 1/34:5/36[d] U 4/16:9/14[e]						3
4. Chen 2007[c]	+	N	200 IU	28, 32, 36 weeks	U 1/45:13/49[e]		U 14/45:4/49[e]	1/45:13/49[e]		33/45:35/44[e]	3
5. Chi 2002	+/−	N	200 IU	28, 32, 36 weeks	0/42:2/43[d] 4/27:10/29[e]		21/69:7/72				3
6. Dai 2004	N	N	200 IU	30, 34, 38 weeks	U 1/86:35/70		U 57/86:1/70				3
7. Guo 2006[c]	N	N	200 IU	28, 32, 36 weeks				2/45:9/43		42/45:33/43	3
8. Han 2003[c]	+/−	N	200 IU	28, 32, 36 weeks	3/43:9/38[d] 21/80:23/52[e]		102/126:0/90	5/126:12/90		121/126:78/90	3
9. Ji 2003	N	N	200 IU	28, 32, 36 weeks	U 3/29:5/31		U 10/29:3/31				2/3[g]
10. Ji 2007	+/−	N	200 IU	28, 32, 36 weeks	3/83:5/84[d] 2/30:10/26[e]			1/83:3/84[d] 1/30:6/26[e]		107/113:83/110	3
11. Jia 2001	+/−	+/−	200 IU	28, 32, 36 weeks	0/25:3/30[d] 1/15:7/16[e] 1/20:10/22[f]						3
12. Li 2003	+/−	N	200 IU	28, 32, 36 weeks	3/56:8/52						4
13. Li 2004	N	N	200 IU	28, 32, 36 weeks	2/57:2/55	4/57:13/55					4
14. Li 2006	N	N	200 IU	28, 32, 36 weeks	13/206:40/253	11/206:37/253					3
15. Liang 2004	N	+	200 IU	28, 32, 36 weeks		5/62:23/60[f]					3
16. Lin 2004	+/−	N	200 IU	28, 32, 36 weeks	7/55:20/62		17/55:5/62	3/53:8/62		33/53:16/62	3
17. Liu 2007[c]	+/−	N	200 IU	28, 32, 36 weeks	1/31:1/34[d] 1/12:2/9[e]		12/31:12/34[d] 4/12:1/9[e]	0/31:1/34[d] 0/12:2/9[e]		24/31:25/34[d] 10/12:4/9[e]	3
18. Luo 2004	N	N	200 IU	28, 32, 36 weeks	U 3/60:13/40	U 5/60:17/40	U 22/60:0/40				3
19. Pan 2006	+/−	N	200 IU	28, 32, 36 weeks	U 2/50:3/50		U 3/50:4/50				3
20. Shi 2009	N	+/−	200 IU	28, 32, 36 weeks	8/146:15/84 8/116:10/43[f]	4/116:5/43[f]					5
21. Su 2000[c]	+/−	N	200 IU	28, 32, 36 weeks	0/22:2/25[d] 3/23:8/18[e]					24/26:17/18	3
22. Sui 2002	N	N	100 IU	28, 32, 36 weeks	0/58:11/52	6/58:18/52	53/58:6/52				3
23. Xing 2003[c]	+/−	+/−	200 IU	28, 32, 36 weeks	0/30:3/25[d] 2/16:6/15[e] 2/22:9/20[f]					27/28:21/24	3
24. Xu 2004[c]	N	N	200 IU	28, 32, 36 weeks	1/45:9/44	0/45:6/44	8/45:1/44	1/45:10/44	0/45:5/44	39/45:30/44	3
25. Xu 2006	+	N	200 IU	28, 32, 36 weeks		U 7/28:20/24[e]					4
26. Yang 2006	+/−	+/−	200IU	28, 32, 36[d]/28, 30, 32, 34, 36, 38[e] weeks	2/46:14/32[d] 12/117:48/90[e]	0/46:0/32[d] 14/117:77/90[e]	10/46:0/32[d] 7/117:0/90[e]				3
27. Yu 2005	N	N	200 IU	28, 32, 36 weeks	U 3/60:13/40						3
28. Yu 2006	+/−	N	200 IU	28, 32, 36 weeks	0/40:2/20[d] 8/15:8/8[e]		10/55:0/28				3
29. Yu 2008	+/−	+/−	200 IU	28, 32, 36 weeks	U 1/28:9/33	U 1/28:7/33					3
30. Yuan 2006	+	N	400 IU	28, 32, 36 weeks	27/118:32/133[e]		0/118:0/133[e]	13/118:17/133[e]		101/118:112/133[e]	4
31. Yue 1999	N	N	200 IU	28, 32, 36 weeks	0/35:3/14		32/35:0/14				4
32. Zhang 2005	+/−	N	200 IU	28, 32, 36[d]/24, 28, 32, 36[e] weeks	2/58:16/49[d] 3/56:19/40[e]						3
33. Zhang 2007	N	N	200 IU	28, 32, 36 weeks	11/163:54/157						3
34. Zheng 2005	N	+	200 IU	28, 32, 36 weeks		U 7/92:28/92[f]					3

35. Zhu 1997	N	N	200 IU	28, 32, 36 weeks	0/68:3/70[d] 6/37:12/32[e]	19/491:48/496		4
36. Zhu 2003	+/−	N	200[d]/400[e] IU	28, 32, 36 weeks	31/491:76/496 7/318:22/304[d] 21/169:49/189[e] 6/58:13/56[f]			4
37. Zhu 2004	+	N	400 IU	28, 32, 36 weeks	5/51:12/54[e]		48/51:45/54	3

HBIG, hepatitis B immunoglobulin; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; N, not indicated; U, umbilical cord blood for data in this RCT.

[a] References are listed in alphabetical order of author name (references 8,10–45).

[b] Ratios are between the HBIG group and control group.

[c] HBIG injection 200 IU in newborns at 0 and 15 days after birth.

[d] Maternal HBsAg-positive.

[e] Maternal HBsAg-positive and HBeAg-positive.

[f] Maternal HBV DNA-positive.

[g] The first number is that originally graded by one of the authors, and the second number is the final grade after discussion among all authors or contact with the authors of the RCT for detailed confirmation.

intrauterine infection and MTCT were defined as neonatal peripheral or umbilical blood HBsAg- or HBV DNA-seropositive at birth and at 9–12 months old, respectively. Protection against HBV was determined by detection of HBsAb at birth and at 9–12 months of age. Secondary outcomes included treatment methods, newborn immune prophylaxis schedules, and adverse effects in both pregnant mothers (such as transaminase increase, intolerance to treatments, complications in pregnancy and during delivery) and their newborns (such as 1-min Apgar score and developmental indices).

2.3. Statistical analysis

Statistical analyses were done by use of Review Manager version 5.0 software, devised by the Cochrane Collaboration. Pooled odds ratios (OR) and 95% confidence intervals (CI) were determined by use of a Mantel–Haenszel random-effects model shown in forest plots. In the case of a cell with zero events in an individual study, the OR was calculated with 0.5 added to the zero cell. Statistical between-study heterogeneity was assessed by Chi-square test and I^2 measurement. Publication bias was assessed by funnel plot. Differences between subgroups were assessed on the basis of the Chi-square statistic. For all tests done, a *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patients

Thirty-seven RCTs on HBIG application in late pregnancy aimed at interrupting HBV MTCT, published in Chinese and English, were included in the final analysis (Figure 1); there were 5900 infants, 3062 in the HBIG treatment group and 2838 in the control group (without intervention or with placebo) (Table 1).[8,10–45]

3.2. Newborn HBsAg seropositivity

Altogether there were 2850 newborns in the HBIG group and 2644 newborns in the control group, included in 32 RCTs. Disregarding maternal HBV DNA status, there were 2730 newborns in the HBIG group and 2598 newborns in the control group. The pooled OR (95% CI) comparing these two groups for newborn HBsAg seropositivity was 0.22 (0.17, 0.29), and a medium level of heterogeneity was observed (I^2 =43%). In the maternal HBeAg-negative subgroup, there were 840 newborns in the HBIG group and 790 newborns in the control group, included in 13 RCTs, with OR (95% CI) being 0.21 (0.13, 0.34) (I^2 = 0%). In the maternal HBeAg-positive subgroup, there were 827 newborns in the HBIG treatment group and 774 newborns in the control group, included in 16 RCTs, with OR (95% CI) being 0.24 (0.15, 0.38) (I^2 = 60%). In the subgroup where maternal HBeAg status was not mentioned (the subgroup named 'others'), there were 1063 newborns in the HBIG group and 1034 newborns in the control group, included in 16 RCTs, with OR (95% CI) being 0.20 (0.12, 0.32) (I^2 = 42%) (Table 2). When maternal HBV DNA-positive, there were 216 newborns in the HBIG treatment group and 141 newborns in the control group, included in four RCTs, with OR (95% CI) being 0.23 (0.12, 0.44) (I^2 = 0%) (Table 2s). Publication bias was shown by a funnel plot (Figure 2).

3.3. Newborn HBV DNA seropositivity

In total there were 1004 newborns in the HBIG group and 893 newborns in the control group who had data on their serum HBV DNA status, included in 13 RCTs. Disregarding maternal HBV DNA

Table 2
Newborn HBV intrauterine infection according to HBsAg positivity

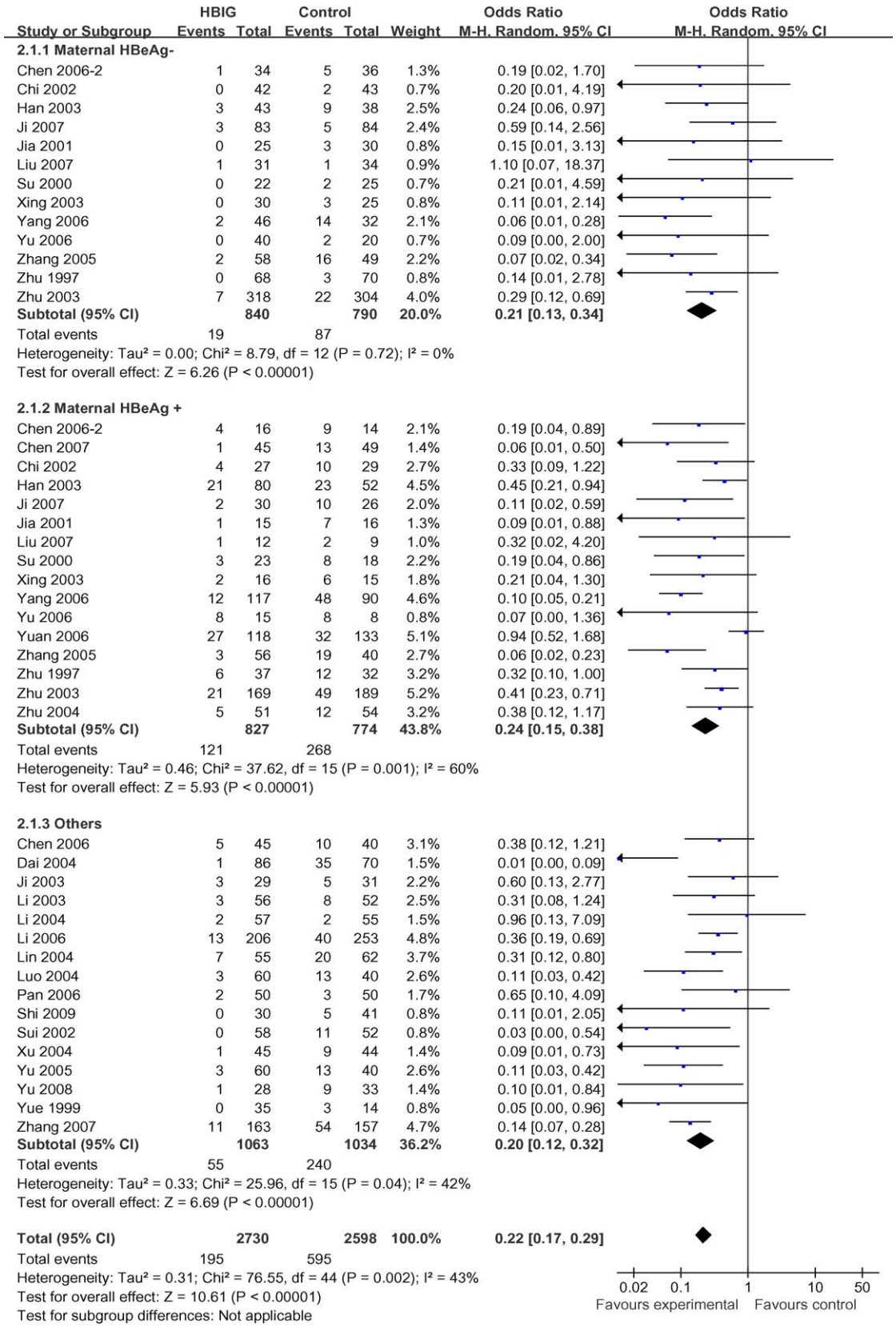
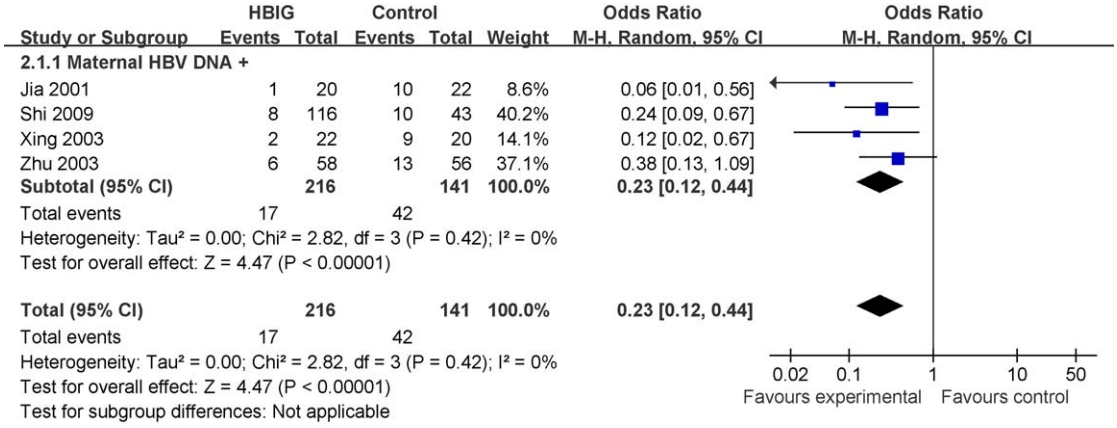


Table 2s
Newborn HBV intrauterine infection according to HBsAg positivity



status, there were 734 newborns in the HBIG group and 698 newborns in the control group. The pooled OR (95% CI) comparing these two groups for newborn HBsAg seropositivity was 0.15 (0.07, 0.30), and a high level of heterogeneity was observed (I^2 = 68%). In the maternal HBeAg-negative subgroup, there were 72 newborns in the HBIG group and 52 newborns in the control group, included in two RCTs, with an OR (95% CI) of 0.36 (0.03, 4.28). In the maternal HBeAg-positive subgroup, there were 163 newborns in the HBIG group and 129 newborns in the control group, included in three RCTs, with an OR (95% CI) of 0.05 (0.02, 0.18) (I^2 = 61%). In the 'others' subgroup, there were 499 newborns in the HBIG group and 517 newborns in the control group, included in seven RCTs, with OR (95% CI) being 0.24 (0.16, 0.38) (I^2 = 0%) (Table 3, Figure 3). When maternal HBV DNA-positive, there were 284 newborns in the HBIG treatment group and 207 newborns in the control group, included in four RCTs, with OR (95% CI) being 0.18 (0.10, 0.32) (I^2 = 0%) (Table 3s).

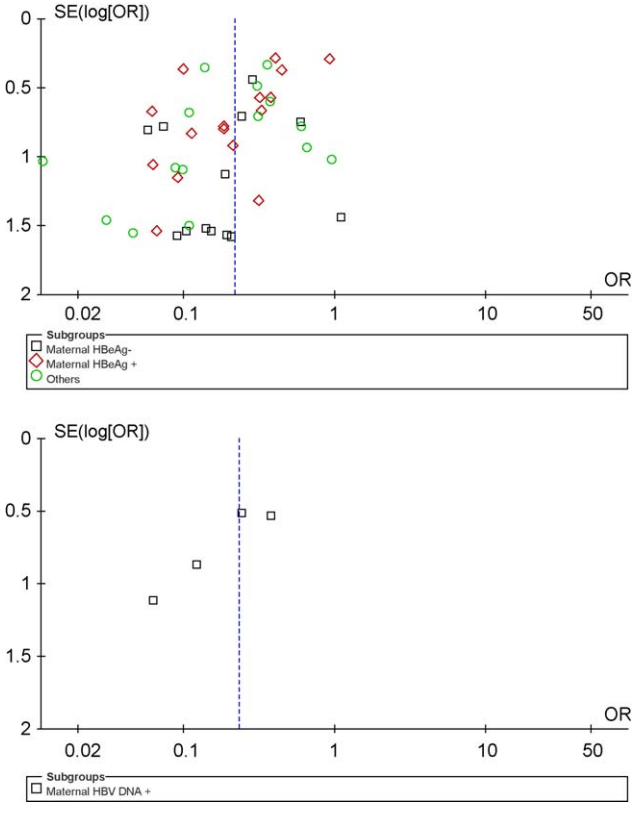


Figure 2. Funnel plots for Table 2 and Table 2s.

3.4. Infant HBsAg seropositivity at 9–12 months

There were 1079 infants in the HBIG group and 1070 infants in the control group who had data on their serum HBsAg status at 9–12 months of age, included in nine RCTs, with a pooled OR (95% CI) of 0.33 (0.21, 0.51) (I^2 = 19%). When maternal HBeAg-negative, there were 114 infants in the HBIG group and 118 infants in the control group, included in two RCTs, with an OR (95% CI) of 0.34 (0.05, 2.18) (I^2 = 0%). When maternal HBeAg-positive, there were 205 infants in the HBIG group and 217 infants in the control group, included in four RCTs, with an OR (95% CI) of 0.21 (0.04, 1.03) (I^2 = 65%). In the 'others' subgroup, there were 760 infants in the HBIG group and 735 infants in the control group, included in five RCTs, with OR (95% CI) being 0.32 (0.21, 0.49) (I^2 = 0%) (Table 4, Figure 4).

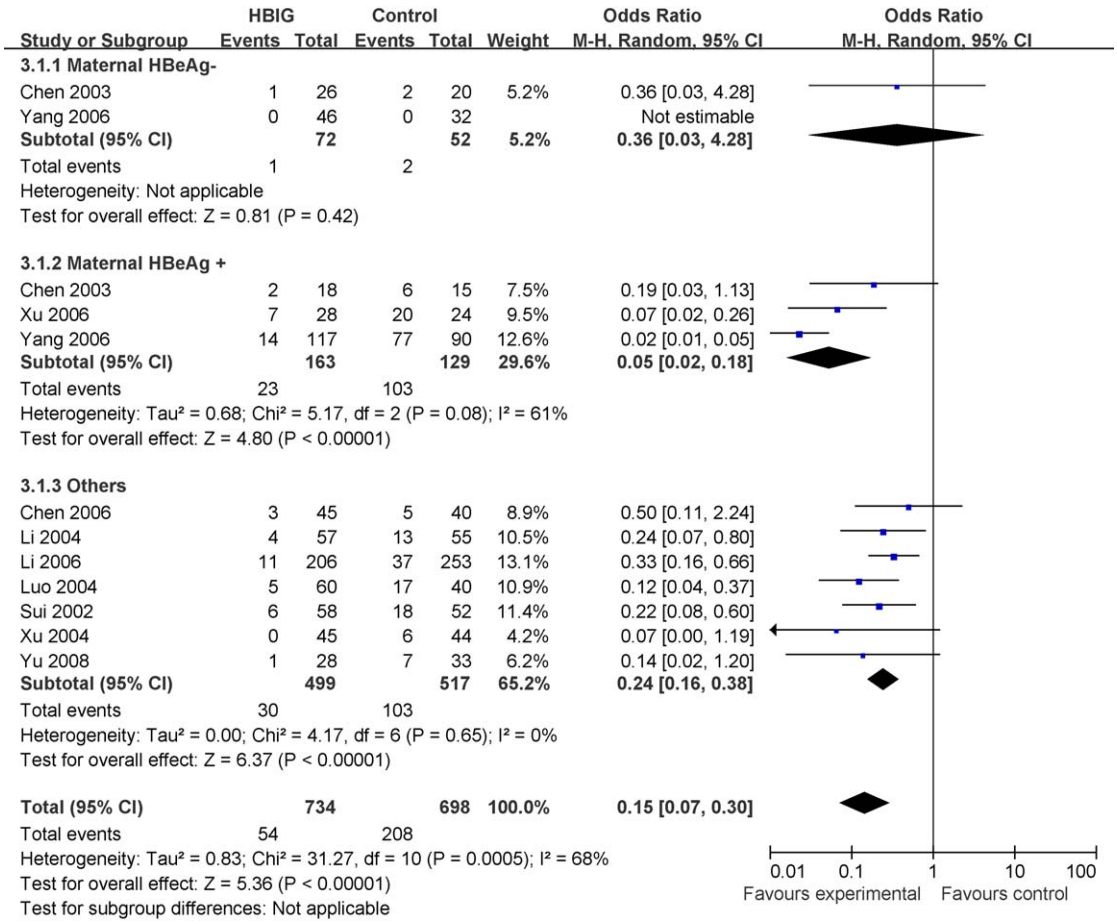
3.5. Newborn HBsAb seropositivity

Altogether 1037 newborns in the HBIG treatment group and 900 newborns in the control group had data on their serum HBsAb status, included in 15 RCTs, with a pooled OR (95% CI) of 11.79 (4.69, 29.61) (I^2 = 79%). When maternal HBeAg-negative, there were 77 newborns in the HBIG group and 66 newborns in the control group, included in two RCTs, with an OR (95% CI) of 3.47 (0.20, 61.54) (I^2 = 73%). When maternal HBeAg-positive, there were 292 newborns in the HBIG treatment group and 281 newborns in the control group, included in four RCTs, with OR (95% CI) being 5.43 (1.98, 14.85) (I^2 = 0%). In the 'others' subgroup, there were 668 newborns in the HBIG treatment group and 553 newborns in the control group, included in 11 RCTs, with OR (95% CI) being 18.34 (5.63, 59.72) (I^2 = 81%) (Table 5, Figure 5).

3.6. Infant HBsAb seropositivity at 9–12 months

There were 693 infants in the HBIG group and 665 infants in the control group who had data on their serum HBsAb status at 9–12 months of age, included in 11 RCTs, with pooled OR (95% CI) being 2.49 (1.55, 4.01) (I^2 = 50%). When maternal HBeAg-positive, there were 175 infants in the HBIG group and 186 infants in the control group, included in three RCTs, with OR (95% CI) being 1.20 (0.52, 2.79) (I^2 = 45%). In the 'others' subgroup, there were 487 infants in the HBIG group and 445 infants in the control group, included in

Table 3
Newborn HBV intrauterine infection according to HBV DNA positivity



eight RCTs, with OR (95% CI) being 4.01 (2.66, 6.06) ($I^2 = 0\%$) (Table 6, Figure 6).

The above analyses showed a generally significant reduction of HBV MTCT and a significantly higher HBV protection rate in the HBIG group both at birth and at 9–12 months after delivery (Table 7). In the short-term (at the time-point of birth), HBIG effectively interrupted HBV intrauterine infection. In the long-term, HBIG effectively interrupted HBV MTCT when HBV carrier mothers had a high HBV degree of infectiousness.

3.7. Secondary outcomes

There were some differences in treatment doses and schedules in the different subgroups. Maternal HBeAg and HBV DNA status representative of the degree of infectiousness were described in a portion of the RCTs (Table 1). Few RCTs reported adverse effects in pregnant mothers or newborns.

4. Discussion

4.1. Diagnosis of HBV intrauterine infection

The diagnoses of HBV intrauterine infection include: (1) serum HBsAg-positive and/or HBeAg-positive, or HBV DNA-positive after birth; (2) serum HBsAg-positive and/or HBeAg-positive, or HBV DNA-positive after birth, lasting more than two months;[46] (3) persistent serum anti-HBc IgM-positive after birth;[47] (4) continuous three out of four serum samples HBsAg-positive, including within 24 h after birth, and at 1, 6, and 12 months of age.[48] All RCTs in our analysis referred to the first diagnosis.

4.2. Interpretation of results

Although in the maternal HBeAg-negative subgroup, and even in the maternal HBeAg-positive subgroup, HBIG treatment had no statistical significance in the interruption of HBV MTCT at 9–12 months of age, HBIG showed its significance in the pooled comparison results. Considering the reduced heterogeneity in the pooled comparison and the relatively smaller number of cases in each subgroup, it might be reasonable to assume that the pooled results apply to those subgroups as well. It is known that although HBeAg indicates a higher degree of infectiousness, there are still certain HBV carriers who are HBeAg-seropositive but have a low degree of infectiousness, and vice versa.[49] HBV DNA is more accurate in predicting the degree of infectiousness, because its seropositivity is proof of HBV active replication. Unfortunately, few RCTs reported MTCT of HBV with regard to maternal HBV DNA status. Because maternal HBeAg and HBV DNA do not always coincide, we reported maternal HBV DNA-positive newborns separately from the pooled analysis to avoid duplication of cases.

4.3. HBIG in interruption of HBV intrauterine infection

HBIG contains high levels of antibody to HBsAg. A prospective study administered multiple HBVac intramuscular injections along with HBIG to HBsAg-positive mothers from 20 weeks of gestation,

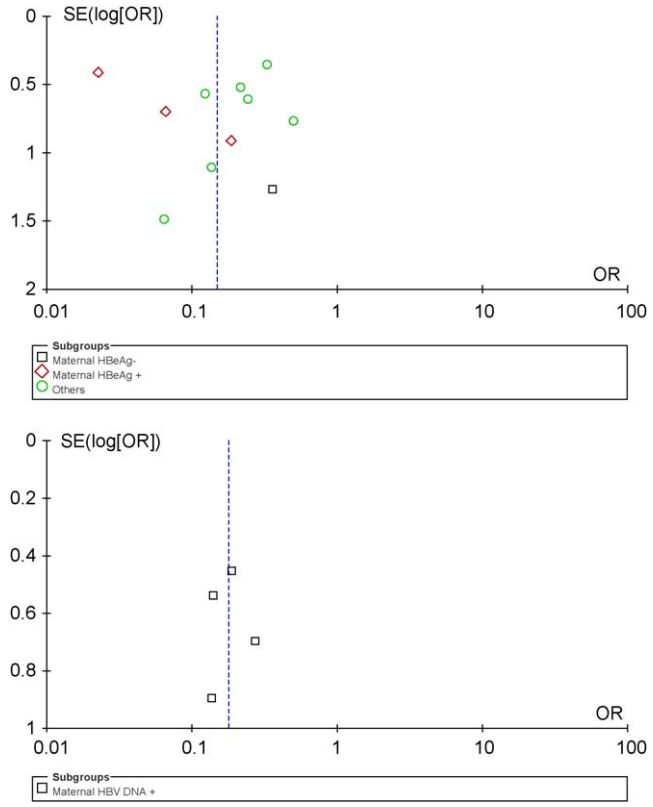


Figure 3. Funnel plots for Table 3 and Table 3s.

and showed effective prevention of HBV intrauterine infection and newborn passive immunization.[50] The possible mechanism is that HBsAb can bind HBsAg, activate the complement system, facilitate humoral immunity, reduce HBV level in pregnant mothers, prevent and reduce the infection of normal cells, and reduce replication of HBV. It might also be related to the passive immunization obtained from pregnant mothers.[51] These mechanisms have been challenged by Xiao et al.[52] and Han et al.[53] The former reported HBIG's efficacy in the interruption of intrauterine infection, but found no significant increase in the newborn HBsAb seropositivity rate. The latter found no significant decrease in maternal HBV DNA load, and none of their newborns obtained HBsAb. Our meta-analysis solved this controversy by showing a significant increase in the newborn HBsAb seropositivity rate and a lower intrauterine infection rate in the HBIG group based on more patients when maternal HBV DNA was also positive.

The biggest controversy is whether 100 or 200 IU of HBIG injections at 1-month intervals are effective in decreasing maternal HBV load or enabling HBIG to enter the fetal circulation through the placenta, because it needs a continuous blood concentration of 100–500 IU/l of HBIG to neutralize HBV in the blood, even after the HBV-producing liver has been replaced by a healthy one.[54] However, several studies have found a significant decrease in maternal HBV DNA[21,28] and HBsAg titer.[39,44] Yu et al.[36] found that an additional injection of 200 IU HBIG at labor onset significantly decreased both maternal HBV DNA and HBsAg titer, and induced newborn HBsAb, compared with the 28–32–36 weeks HBIG treatment group or control group. They also showed that within 3–7 days after HBIG injection, both maternal HBV DNA and HBsAg decreased, while at 1 month after HBIG injection, maternal HBV DNA and HBsAg returned to the level before injection. Based on these findings, they proposed that the interruption of HBV intrauterine infection with HBIG was mainly due to HBIG transportation through the placenta, and less likely due to the reduced maternal HBV load.

Another concern is whether massive HBIG injections in HBV carrier mothers might cause HBV mutation, which would be resistant to current HBVac. Yu et al.[36] showed that there was no significant increase in the HBV mutation rate in HBV-infected newborns in the HBIG group. There was no report of HBV mutation in patients treated with HBIG at a total dosage of less than 20 000 IU and within 2 months. Since HBV intrauterine transmission occurs mainly during the third trimester, and most of the fetal organs have developed into shape by that time, which may be influenced least during pregnancy,[21] it is reasonable to apply HBIG in pregnant mothers in late pregnancy with a limited amount and for a limited duration.

Few RCTs reported sufficiently on adverse events. It should also be noted that HBIG and the plasma-derived HBVac have the potential for transmission of blood-borne infections. RCTs may overlook adverse events because of the relatively low numbers of participants or poor reporting of adverse events.

4.4. Influencing factors

Clinically, HBV infection is diagnosed by HBsAg seropositivity or HBV DNA seropositivity, and patients in these two categories do not have complete coincidence. To avoid this, the exact number of

Table 3s
Newborn HBV intrauterine infection according to HBV DNA positivity

Study or Subgroup	HBIG Events	HBIG Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 Maternal HBV DNA +						
Chen 2003	3	14	8	12	10.8%	0.14 [0.02, 0.79]
Liang 2004	5	62	23	60	29.8%	0.14 [0.05, 0.40]
Shi 2009	4	116	5	43	17.7%	0.27 [0.07, 1.06]
Zheng 2005	7	92	28	92	41.7%	0.19 [0.08, 0.46]
Subtotal (95% CI)		**284**		**207**	**100.0%**	**0.18 [0.10, 0.32]**
Total events	19		64			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.89 (P < 0.00001)						
Total (95% CI)		**284**		**207**	**100.0%**	**0.18 [0.10, 0.32]**
Total events	19		64			
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 5.89 (P < 0.00001)						
Test for subgroup differences: Not applicable						

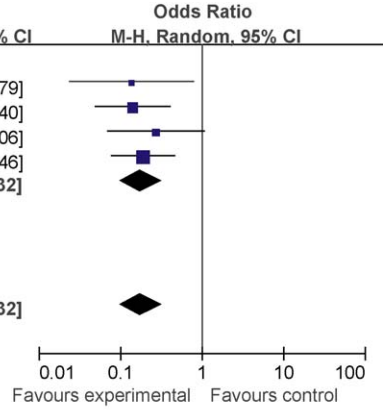
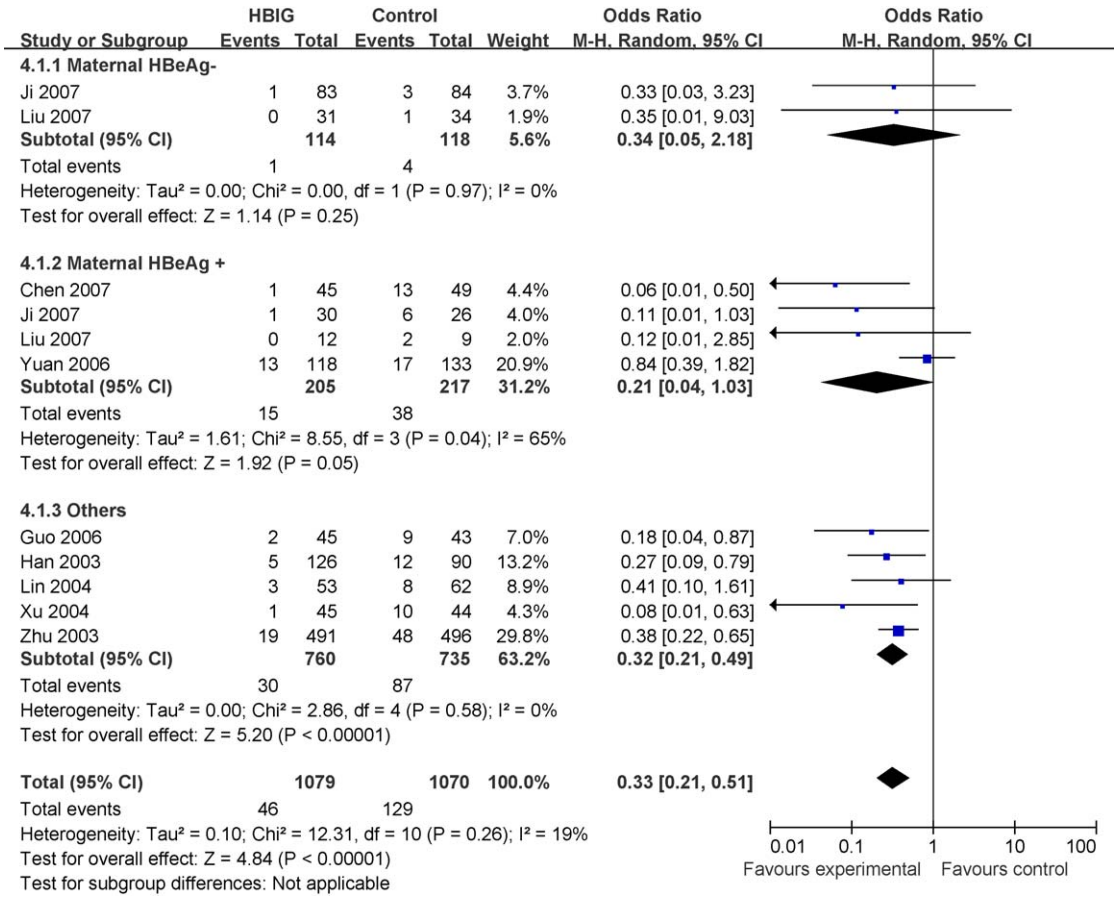


Table 4
Infant HBV infection at 9–12 months according to HBsAg positivity



HBV infection cases should be reported as HBsAg-positive and/or HBV DNA-positive, as was reported by Li et al.,[8] which is more practical and accurate in diagnosing HBV infection. Many studies have shown that the decisive factor in HBV MTCT is maternal HBV viremia level.[55] Maternal serum HBeAg or HBV DNA status in each study should also be considered. Ngui et al.[56] showed that when maternal HBV DNA was higher than 10^8 copies/ml, the intrauterine infection rate was significantly higher.

In our analysis, the schedules of joint immune prophylaxis with HBVac and HBIG injections in different studies were commonly recommended.[3–5] Since most infant HBV infection occurs before 1 year of age,[57] all studies tested peripheral serum of these infants at 9–12 months of age to determine the results of HBV MTCT and joint immune prophylaxis. The effective component in HBVac is deactivated HBsAg protein, which is the object of HBIG, and this might influence the immunogenicity of HBVac. However, Beasley et al.[58] argued that the existence of passive antibody would not inhibit the immune response to the vaccine.

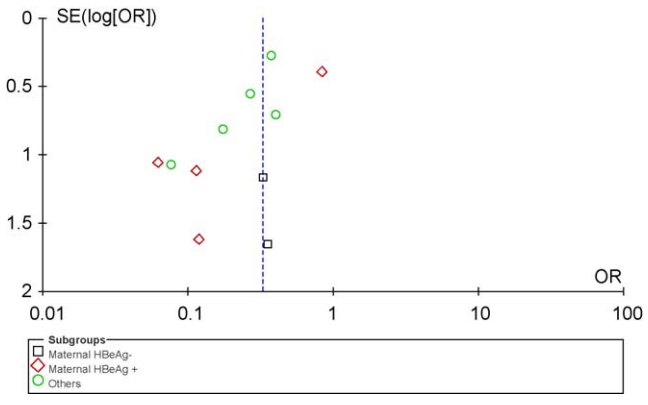


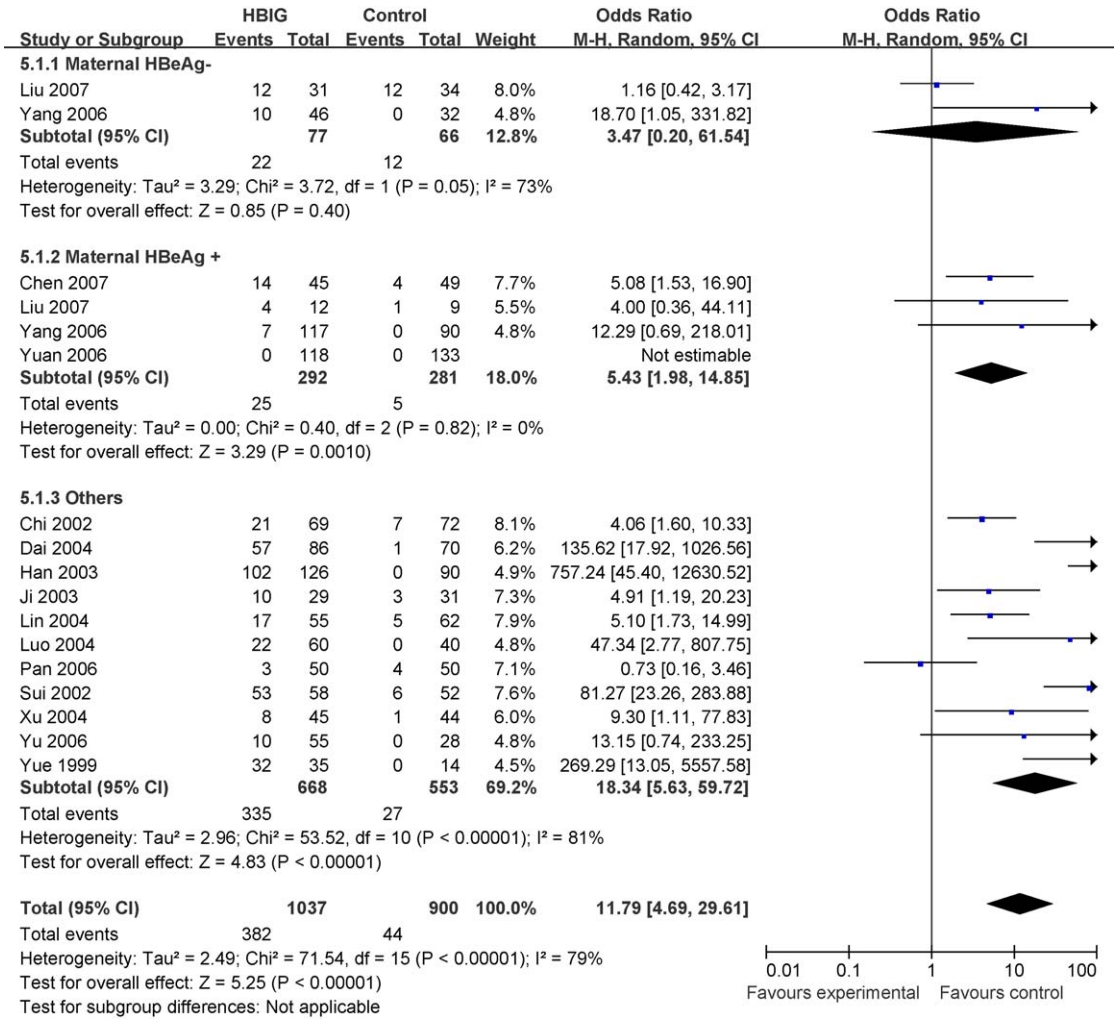
Figure 4. Funnel plot for Table 4.

4.5. Bias, heterogeneity, and quality of enrolled RCTs

The included RCTs with a Jadad score of 3 points or above were all carried out in China, where the HBV prevalence might be different from that in other regions. The quality of journals should also be taken into account, although all the included journal sources were peer-reviewed. We searched studies only in English and Chinese languages, which might render a selection bias. Publication bias, which is due to a desire to publish positive or effective results by journals or researchers, can be shown by funnel plot,[59] and should also be taken into consideration. In our analysis, the estimated OR is likely biased in favor of the intervention group due to publication bias.

The heterogeneity of each analysis ranged from low (0%) to high (79%). Theoretically, heterogeneity would decrease if subgroups were divided according to risk factors.[60] However, even though heterogeneity did decrease in the maternal HBeAg-negative subgroup, it increased in the HBeAg-positive group and some of the 'other' group. Again this can be explained by the lower value of HBeAg as an indicator of degree of infectiousness compared with HBV DNA. The heterogeneity was low with regard to maternal HBV

Table 5
Newborn HBsAb positivity



DNA seropositivity, suggesting that when allocating HBV carrier mothers into treatment or control groups in future RCTs, their HBV DNA status should also be considered to make the efficacy of HBIG more convincing. Some analyses included few RCTs and a small number of newborns or infants, which might explain why dividing into subgroups improved heterogeneity but lowered the power of statistical tests. In order to evaluate the application of HBIG in pregnant mothers, more RCTs that accurately describe maternal HBV DNA status (ideally quantitatively) are needed for further investigations and more convincing results.

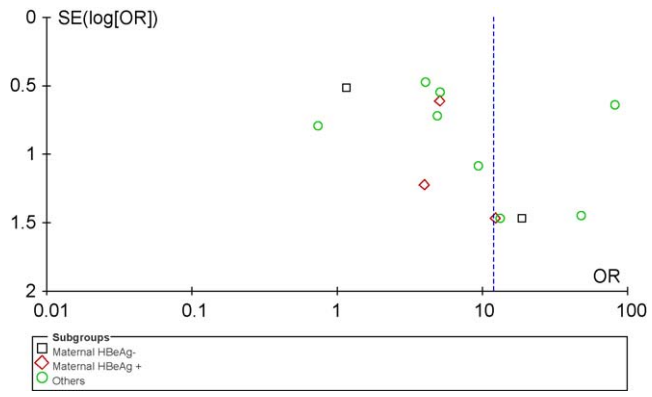


Figure 5. Funnel plot for Table 5.

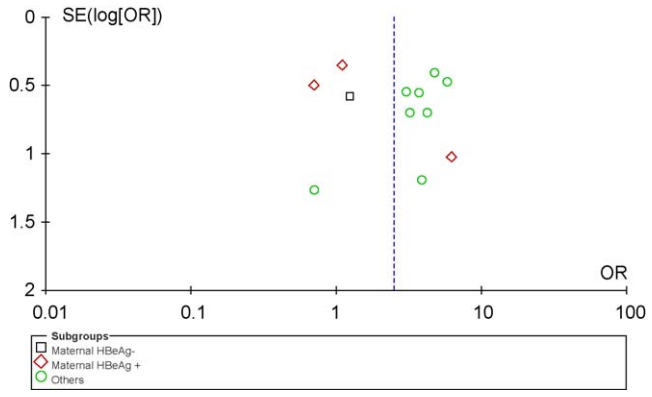


Figure 6. Funnel plot for Table 6.

Table 6
Infant HBsAb-positive at 9–12 months

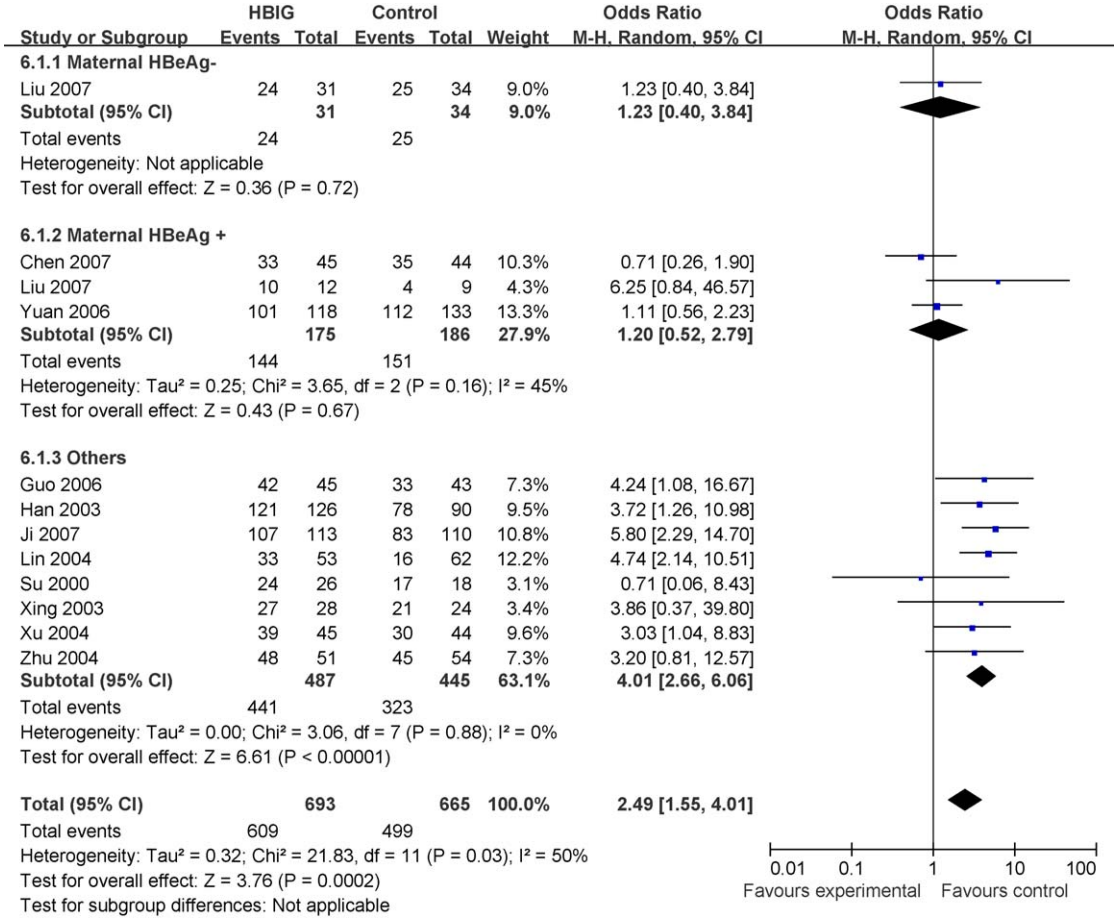


Table 7
Summary of meta-analysis results

Results	Maternal HBsAg-pos and HBeAg-neg[a]				HBsAg-pos and HBeAg-pos				Others					HBsAg-pos and HBV DNA-pos			
	OR (95% CI)	No. RCTs[b]	Cases[c]	I^2	OR (95% CI)	No. RCTs[b]	Cases[c]	I^2	OR (95% CI)	No. RCTs[b]	Cases[c]	I^2	I^{2d}	OR (95% CI)	No. RCTs[b]	Cases[c]	I^2
Newborn																	
HBsAg-pos	0.21 (0.13, 0.34)	13	1630	0%	0.24 (0.15, 0.38)	16	1601	60%	0.20 (0.12, 0.32)	16	2097	42%	43%	0.23 (0.12, 0.44)	4	357	0%
HBV DNA-pos	*0.36 (0.03, 4.28)*	*2*	*124*	-	0.05 (0.02, 0.18)	3	292	61%	0.24 (0.16, 0.38)	7	1016	0%	68%	0.18 (0.10, 0.32)	4	491	0%
HBsAb-pos	*3.47 (0.20, 61.54)*	*2*	*143*	73%	5.43 (1.98, 14.85)	4	573	0%	18.34 (5.63, 59.72)	11	1221	81%	79%	-			
Infants																	
HBsAg-pos	*0.34 (0.05, 2.18)*	*2*	*232*	0%	0.21 (0.04, 1.03)	4	422	65%	0.32 (0.21, 0.49)	5	1495	0%	19%	-			
HBV DNA-pos	-				-				0.08 (0.00, 1.47)	1	89	-	-	-			
HBsAb-pos	*1.23 (0.40, 3.84)*	*1*	*35*	-	1.20 (0.52, 2.79)	3	361	45%	4.01 (2.66, 6.06)	8	932	0%	50%	-			

OR, odds ratio; CI, confidence interval; RCT, randomized control trial; HBIG, hepatitis B immunoglobulin; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody.

[a] Data in italic showed no significant HBIG HBV interrupting rate (indicated by OR (95% CI) of HBIG vs. control group in HBsAg or HBV DNA seropositivity) or HBV protection rate (indicated by HBsAb seropositivity). However, those data included fewer RCTs and much fewer cases, whose results should be further evaluated.

[b] Number of RCTs included.

[c] Cases in both the HBIG group and the control group.

[d] Pooled I^2.

In summary, our meta-analysis provides strong evidence that multiple small doses of HBIG injection in late pregnancy, along with joint immune prophylaxis beginning after birth, is effective and safe in the interruption of HBV intrauterine infection and MTCT in HBV carrier mothers with a high degree of infectiousness compared with joint immune prophylaxis alone. For asymptomatic HBV carrier mothers, we also recommend the above-mentioned HBIG administration as a complementary treatment to the routine immune prophylaxis in their newborns, beginning after birth.

Conflict of interest

There was no conflict of interest concerning this paper; no competing interest declared; no funding source. No ethical approval was required for this paper.

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